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AN ANTIMALARIAL ALKALOID FROM HYDRANGEA. XVI. SYNTHESIS OF 5-, 6-, 7-, AND 8-DERIVATIVES WITH TWO DIFFERENT SUBSTITUENTS

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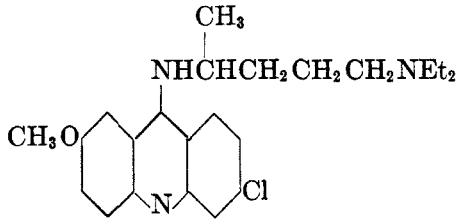
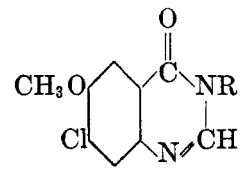
Studies of the effect on antimalarial activity and chemotherapeutic index by substitution in the benzene ring of the *dl*-form of the Hydrangea alkaloid have been continued. The synthesis of eight of the possible twelve methylchloro and three of the methoxychloro derivatives are herein described.

Some of the dichloro derivatives of the *dl*-alkaloid have high activity, but low chemotherapeutic index (1).[1] The methylchloro derivatives[2] were synthesized to see if this high activity could be maintained and the index increased. This goal was not realized, in fact, the opposite effect was obtained, namely, lowering of the activity instead of increase in index. The best compound obtained in this series was the 5-chloro-6-methyl which had a quinine coefficient of about 70 and an index of 10, about the same as the 5-chloro derivative.[1]

One of the best compounds of the acridine series of antimalarials is Atabrine (I). Here the chloro is related 7 to the hetero-nitrogen and the methoxy 6. The corresponding derivative of the alkaloid would be the 6-methoxy-7-chloro (II).



I



II

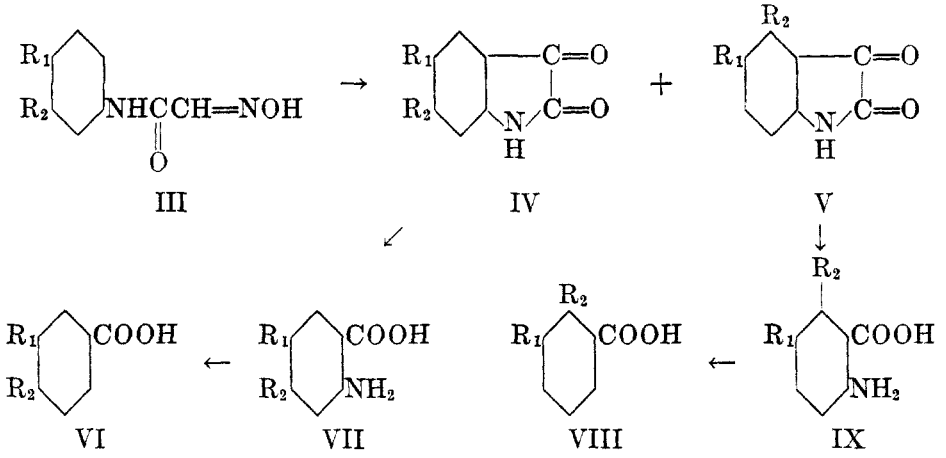
This compound was about $\frac{2}{3}$ as active as the *dl*-alkaloid and had the same chemotherapeutic index. Thus, there appears to be no correlation between structure and activity in the acridine series which can be carried over to the 4-quinazolone nucleus. The 5-chloro-6 (and 8)-methoxy derivatives had a low order of activity.

The eleven 4-quinazolones necessary for synthesis of the *dl*-alkaloid derivatives by the usual method (3) were all obtained *via* the proper isatins and anthranilic acids using the Sandmeyer procedure (4). In three cases ring closure of the α-isonitrosoacetanilides, III, led to a mixture of two isatins, IV and V. These

[1] The biological data will be reported elsewhere by Dr. R. Hewitt and co-workers as paper XIII of this series (2).

[2] The 5-Cl-7-Me, 7-Cl-5-Me, 8-Cl-5-Me, and 8-Cl-7-Me derivatives were not prepared since assay data accumulated on substituents in these positions with other groups (2) made it probable that these would be poor antimalarials.

were separated by fractional acidification of an alkaline solution. The structures of the anthranilic acids, VII and IX, were demonstrated by deamination to the substituted benzoic acids, VI or VIII. In each case the angular substituted isatin, V, always precipitated first.[3] For example cyclization of 3-chloro-4-methyl-α-isonitrosoacetanilide (IIIa) afforded the isatin Va, m.p. 242–244°, in the first fractions and IVa, m.p. 256–258°, in the later fractions. Peroxide oxidation of the



a series: $R_1 = CH_3$; $R_2 = Cl$
b series: $R_1 = Cl$; $R_2 = CH_3$
c series: $R_1 = CH_3O$; $R_2 = Cl$

lower-melting isatin gave the unknown 5-methyl-6-chloroanthranilic acid (IXa), m.p. 156–157° dec. The latter on deamination afforded the unknown 2-chloro-3-methylbenzoic acid, m.p. 138–140°. If this isatin had structure IVa, then the known 3-methyl-4-chlorobenzoic acid (VIa), m.p. 209° (6), would have resulted by this sequence. Similar structure proofs were also used in the b and c series.

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EXPERIMENTAL

4 (and 6)-Chloro-5-methylisatin (Va and IVa). The crude isatin mixture obtained by cyclization of 28.2 g. of 3-chloro-4-methyl-α-isonitrosoacetanilide (Table I) with 132 cc. of 96% sulfuric acid and 13 cc. of water (9), was dissolved in 500 cc. of water by the addition of 125 cc. of 10% sodium hydroxide. Some insoluble oil was removed by filtration through Celite. To the stirred solution was added 12 *N* hydrochloric acid to turbidity, then 2 cc. more. The precipitate was collected. Four more 2-cc. additions were made and the precipitate collected each time. The solution was then strongly acidified for a sixth fraction. The separation of isatin IVa from Va was followed by mixed m.p. and the split came between fractions 4 and 5. Recrystallization of the combined first four fractions from acetic acid gave 6.4 g. (25%) of the red isatin, IVa, m.p. 240–241°. Further recrystallization raised the m.p. to 242–244° (see Table II).

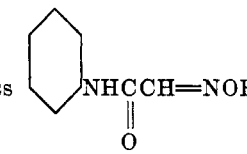
[3] This was also true for $R_1 = R_2 = CH_3$ and $R_1 + R_2 = -(CH_2)_4-$ (1). The rule also holds for $R_1 = H$ and $R_2 = Cl$ (5).

Fractions 5 and 6 were combined; yield, 2.2 g. (10%) of Va, m.p. 243–245° dec. Recrystallization from acetic acid gave orange crystals, m.p. 256–258° (see Table II).[4]

The red isatin, IVa, was converted to 5-methyl-6-chloroanthranilic acid (IXa) (Table III), then deaminated (14). A mixture of 200 mg. of this acid, 2.4 cc. of 50% hypophosphorous acid, and 2 cc. of water was warmed to complete solution, then cooled in an ice-salt bath. A solution of 80 mg. of sodium nitrite in 0.8 cc. of water was added dropwise over a period of ten minutes during which nitrogen was evolved and erystals separated. After four hours at 0°, the mixture was diluted with ice-water and filtered. The solid was washed with water; yield, 140 mg. (76%) of 2-chloro-3-methylbenzoic acid (VIIIa), m.p. 137–138°. Recrystallization from heptane afforded white crystals, m.p. 138–140°.

Anal. Calc'd for $C_8H_7ClO_2$: C, 56.3; H, 4.14.
Found: C, 56.6; H, 4.37.

TABLE I

SUBSTITUTED α-ISONITROSO ACETANILIDES 

R GROUPS	BOIL PERIOD (min.)	YIELD, %	M.P., °C.	LIT. M.P., °C. (ref.)
3-Cl-4-Me[a]	5	67	164–167 d.	177 (4)
5-Cl-2-Me	3	79	143–145 d.	148 (4)
4-Cl-3-Me[b]	10	88	175–177	183 (4)
4-Cl-2-Me	3	55[c]	154–157 d.	167 (4)
3-Cl-2-Me	10	79	153–154[d]	[e]
2-Cl-4-Me[g]	5	62	183–184[f]	188 (4)
3-Cl-4-CH_3O[h]	7	80	207–209 d.[i]	[j]
5-Cl-2-CH_3O	10	56	162–175 d.[f]	182 (4)

[a] For amine source see ref. (7). [b] Amine obtained by sulfuryl chloride chlorination of acet-*m*-toluidide in acetic acid followed by deacetylation in 64% over-all yield (8). [c] Crude product partially purified by solution in 5% sodium hydroxide, filtration and acidification. [d] Recrystallized from toluene. [e] *Anal.* Calc'd for $C_9H_9ClN_2O_2$: C, 50.9; H, 4.27; N, 13.2. Found: C, 50.8; H, 4.63; N, 13.4. [f] Crude product leached with toluene. [g] Amine obtained by sulfuryl chloride chlorination of acet-*p*-toluidide in acetic acid followed by deacetylation in 50% over-all yield (8). [h] Amine obtained by sulfuryl chloride chlorination of acet-*p*-anisidide followed by hydrolysis (yield, 27%). [i] Recrystallized from dilute alcohol. [j] *Anal.* Calc'd for $C_9H_9ClN_2O_3$: C, 47.3; H, 3.96; N, 12.2. Found: C, 47.4; H, 4.16; N, 12.2.

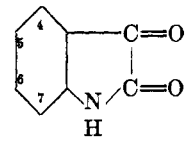
6-Chloro-5-methylisatin by this sequence would give 3-methyl-4-chlorobenzoic acid (VIa), m.p. 209° (6).

5-Chloro-4 (and 6)-methylisatin (Vb and IVb). The crude isatin from 75.4 g. of 3-methyl-4-chloro-α-isonitrosoacetanilide was fractionally precipitated from an alkaline solution as described for IVa and Va. Fractions 1–3 were Vb and fractions 4–5 were IVb[4] (see Table II for additional data). The structures were again proven by deamination of 4-methyl-5-chloroanthranilic acid (VIIb) to 3-chloro-4-methylbenzoic acid, m.p. 193–194°, in 71% yield as described for 2-chloro-3-methylbenzoic acid. Claus and Davidson (15) record m.p. 199° for 3-chloro-4-methylbenzoic acid. The isomeric 5-chloro-4-methylisatin (Vb) would form 2-methyl-3-chlorobenzoic acid, m.p. 159° (16), by this sequence.

[4] It is probable that this fractionation could be more simply effected by partial acidification with acetic acid (1).

TABLE II

ISATINS

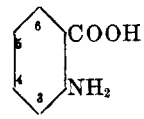


R GROUPS[a]	COLOR	YIELD, %	M.P., °C.	ANALYSIS					
				Calc'd			Found		
				C	H	N	C	H	N
4-Cl-5-Me	Red	25[b]	242–244	55.3	3.09	7.17	55.5	3.62	7.63
4-Cl-7-Me	Orange	99	266–274[c]						
5-Cl-4-Me	Or-red	35[b]	226–227	55.3	3.09	7.17	55.3	3.36	7.40
5-Cl-6-Me	Yel-or.	19[b]	264–266	55.3	3.09	7.17	55.3	3.39	7.22
5-Cl-7-Me	Orange	94	253–258[d]						
6-Cl-5-Me	Orange	10[b]	256–258	55.3	3.09	7.17	55.2	2.72	7.32
6-Cl-7-Me	Orange	95	228–234 d.[e]						
7-Cl-5-Me	Maroon	86	158–162[f]						
4-Cl-5-CH_3O	Red	14[b]	261–262	51.0	2.87	6.62	51.2	3.28	6.76
4-Cl-7-CH_3O	Maroon	96	238–240[g]						
6-Cl-5-CH_3O	Red	45	243–244	51.0	2.87	6.76	51.0	3.21	7.00

[a] These isatins were prepared by cyclization of the isonitrosoacetanilides of Table I with 1:10 H_2O:H_2SO_4 in the usual manner (9). [b] For separation and identification of the two isomers see experimental. [c] Lit. m.p. 273° (4). [d] Lit. m.p. 265° (4). [e] Lit. m.p. 245° (10). [f] Lit. m.p. 180° (11). [g] Lit. m.p. 242° (4).

TABLE III

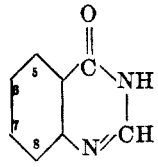
ANTHRANILIC ACIDS



R GROUPS[a]	YIELD, %	M.P., °C. dec.	ANALYSIS					
			Calc'd			Found		
			C	H	N	C	H	N
6-Cl-5-Me	72	156–157[b]	51.7	4.33	7.55	51.7	4.54	7.54
6-Cl-3-Me	31	167–168[c]						
5-Cl-6-Me	68	155–157[d]			7.55			7.50
5-Cl-4-Me	95	205–207[e]						
5-Cl-3-Me	90	228–229[d]	51.7	4.33	7.55	52.0	4.53	7.50
4-Cl-5-Me	77	210–211[d]	51.7	4.33	7.55	51.5	4.45	7.36
4-Cl-3-Me	78	211–212[d]	51.7	4.33	7.55	51.3	4.50	7.95
3-Cl-5-Me	81	208–209[f]	51.7	4.33	7.55	51.3	4.51	7.86
6-Cl-5-CH_3O	70	186[g]						
6-Cl-3-CH_3O	60	145–146	47.6	4.00	6.94	47.2	4.45	7.46
4-Cl-5-CH_3O	89	205–206[g]	47.6	4.00	6.94	48.0	4.26	7.12

[a] These compounds prepared by alkaline peroxide oxidation of the isatins of Table II as described for 3-chloroanthranilic acid (12). [b] Recrystallized from ethyl acetate-heptane. [c] Could not be purified. Crude carried to Table IV. [d] Recrystallized from toluene. [e] Recrystallization from toluene gave m.p. 220–221° dec.; lit. m.p. 220° (13). [f] Recrystallized from heptane. [g] Recrystallized from dilute alcohol.

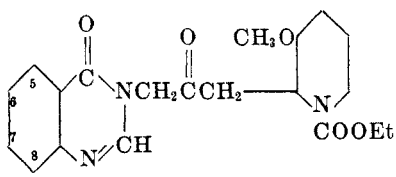
TABLE IV



R GROUPS[a]	YIELD, %	M.P., °C.	ANALYSIS					
			Calc'd			Found		
			C	H	N	C	H	N
5-Cl-6-Me	81	248–249 d.[b]	55.6	3.63	14.4	55.6	4.37	14.2
5-Cl-8-Me	44[c]	276–278[d]	55.6	3.63	14.4	55.8	3.86	14.6
6-Cl-5-Me	78	274–276[d]	55.6	3.63	14.4	55.5	4.14	14.4
6-Cl-7-Me	82	258–260[d]	55.6	3.63	14.4	55.1	3.68	14.5
6-Cl-8-Me	63	307–308[b]	55.6	3.63	14.4	55.2	3.89	14.3
7-Cl-6-Me	78	248–249 d.[b]	55.6	3.63	14.4	55.6	4.37	14.2
7-Cl-8-Me	83	260–261 d.[d]	55.6	3.63	14.4	55.3	3.84	14.1
8-Cl-6-Me	83	298–300[b]	55.6	3.63	14.4	55.0	3.97	14.3
5-Cl-6-CH_3O	66	233–235 d.[e, f]	49.3	3.67	12.7	49.4	3.87	12.3
5-Cl-8-CH_3O	84	311-313 d.[b]	51.3	3.45	13.3	51.3	3.90	13.7
7-Cl-6-CH_3O	89	262–264[d, f]	49.3	3.67	12.7	49.3	3.93	12.3

[a] These compounds obtained by formamide fusion of the anthranilic acids of Table III as described for 8-chloro-4-quinazolone (12). [b] Recrystallized from Methyl Cellosolve. [c] Crude product leached with methanol. [d] Recrystallized from absolute alcohol. [e] Recrystallized from Methyl Cellosolve-water. [f] Hemihydrate.

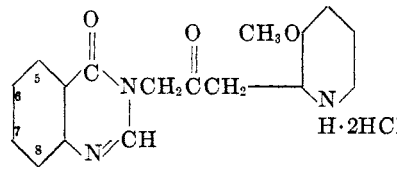
TABLE V



R GROUPS[a]	YIELD, %	M.P., °C.	ANALYSIS FOUND		
			C	H	N
5-Cl-8-Me[b]	33	140–142	57.7	6.26	9.60
6-Cl-5-Me	30	134–136	57.6	6.15	9.55
6-Cl-7-Me	26	140–141	57.7	6.26	9.71
6-Cl-8-Me	49	128	58.3	6.16	9.69
7-Cl-6-Me	40	151–152	58.1	6.03	9.83
8-Cl-6-Me	34	174–176	58.0	6.10	9.53
5-Cl-8-CH_3O[c]	23	145–146	55.8	6.13	9.62

[a] These compounds prepared by condensation of the 4-quinazolones in Table IV with 1-carbethoxy-2-(γ-bromoacetonyl)-3-methoxypiperidine (3). Those not listed were oils and were carried to Table VI. [b] *Anal.* Calc'd for $C_{21}H_{26}ClN_3O_5$: C, 57.8; H, 5.97; N, 9.65. [c] *Anal.* Calc'd for $C_{21}H_{26}ClN_3O_6$: C, 55.9; H, 5.77; N, 9.32.

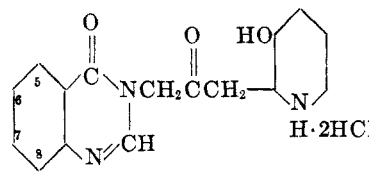
TABLE VI



R GROUPS[a]	YIELD[b] %	M.P., °C. dec.	HYDRATE	ANALYSIS					
				Calc'd			Found		
				C	H	N	C	H	N
5-Cl-6-Me	7.9	226	none	49.6	5.50	9.64	49.1	5.80	9.79
5-Cl-8-Me	8.4	213	hemi	48.4	5.61	9.42	48.5	5.86	9.58
6-Cl-5-Me	12	245–248	mono	47.6	5.72	9.25	47.9	4.84	9.82
6-Cl-7-Me	15	222	hemi	48.4	5.61	9.42	48.8	5.61	9.88
6-Cl-8-Me	12	240	none	49.6	5.50	9.64	49.1	5.21	9.79
7-Cl-6-Me	13	222–223	none	49.6	5.50	9.64	49.0	5.66	10.1
7-Cl-8-Me	14	240	hemi	48.4	5.61	9.42	48.4	5.68	9.36
8-Cl-6-Me	9.5	211	hemi	48.4	5.61	9.42	48.4	6.12	9.34
5-Cl-6-CH_3O	12	227	hemi	46.8	5.47	9.10	46.6	5.15	8.47
5-Cl-8-CH_3O	14	201–202	mono	45.9	5.57	8.93	46.2	5.44	9.09
7-Cl-6-CH_3O	20	205	mono	45.9	5.57	8.93	45.7	5.55	9.32

[a] Prepared by 6 *N* hydrochloric acid hydrolysis of compounds in Table V (3). [b] Based on original x-R-4-quinazolone.

TABLE VII



R GROUPS[a]	YIELD, %	M.P., °C. dec.	HYDRATE	ANALYSIS					
				Calc'd			Found		
				C	H	N	C	H	N
5-Cl-6-Me	85	235	di	44.5	5.67	9.17	44.1	4.98	9.14
5-Cl-8-Me	66	232	mono	46.4	5.44	9.54	46.9	5.68	9.41
6-Cl-5-Me	62	245–250	mono	46.4	5.44	9.54	46.5	5.00	10.2
6-Cl-7-Me	56	232	mono	46.4	5.44	9.54	46.1	5.25	9.74
6-Cl-8-Me	61	228	hemi	47.3	5.33	9.73	47.2	5.15	9.60
7-Cl-6-Me	71	229	sesqui	45.4	5.56	9.35	45.9	5.61	9.45
7-Cl-8-Me	59	246	hemi	47.3	5.33	9.73	47.2	5.68	10.2
8-Cl-6-Me	71	172	di	44.5	5.67	9.17	44.3	5.65	9.28
5-Cl-6-CH_3O[b]	79	230	di	43.0	5.48	8.86	42.3	4.75	9.05
5-Cl-8-CH_3O[b]	66	218–219	none	45.3	4.93	6.92[c]	45.4	5.58	6.90[d]
7-Cl-6-CH_3O[b]	72	181	mono	44.7	5.25	6.80[c]	44.3	5.37	7.84[d]

[a] Compounds prepared by 48% hydrobromic acid hydrolysis of compounds in Table VI (3). [b] Methoxyl analysis showed one methoxyl still present. [c] Calc'd for methoxyl. [d] Found for methoxyl.

4 (and 6)-Chloro-5-methoxyisatin (Vc and IVc). Similarly, fractionation of the crude isatin mixture from 3-chloro-4-methoxy-α-isonitrosoacetanilide gave Vc in fractions 1–3 and IVc in the later fractions.[4] Oxidation of IVc to 4-chloro-5-methoxyanthranilic acid (VIIc) followed by deamination gave 3-methoxy-4-chlorobenzoic acid (VIc) in 93% yield, m.p. 210–211°; lit. m.p. 211° (17). The isomeric Vc would have led to 2-chloro-3-methoxybenzoic acid, m.p. 160° (17).

SUMMARY

The syntheses of eleven derivatives of the *dl*-form of the Hydrangea alkaloid containing chloro and methyl or chloro and methoxyl groups on the benzene ring are described, all of which are active antimalarials.

PEARL RIVER, N. Y.

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